REMARKS

This Reply is responsive to the Office Action dated January 10, 2002. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

Claims 8, 10, 11, 13, 15 and 16 have been amended herein to indicate that the claimed DNA encodes a protein having serine-tyrosine-glycine corresponding to position Nos. 65-67 of SEQ ID No. 1 (claims 1 and 15), or serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His (claims 10, 11, 13 and 16). Support for these amendments may be found in the paragraph bridging pages 2 to 3 of the application, which discloses that the amino acids at position Nos. 65-67 form an imidazolidine ring oxidatively which serves as a chromophore. Further, it is disclosed in the specification at Tables 4-6 and the accompanying discussion thereof at pages 30-32 that the tyrosine residue corresponding to position 66 of the grouping may be substituted by histidine with the resulting protein still retaining fluorescence. No prohibited new matter is added by way of any of these amendments.

Further, a substitute sequence listing is attached hereto. This sequence listing is being submitted in view of Applicants' recent realization that the sequence for the blue fluorescence protein at pages 4-5 of the specification was not included in the previous sequence listing. The sequence is included in the attached substitute sequence listing as SEQ ID No. 15, and the specification has been amended accordingly.

Turning now to the Office Action, in view of the objection to the Drawings, new Drawings are attached hereto for the Draftsperson's consideration.

Claims 8, 10, 11, 13 and 15-20 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking description in the specification. According to the Office Action, the claims

encompass a genus of fluorescent proteins described by insufficient limitations on structure or function, and the specification allegedly discloses no identifying characteristics that would allow one to recognize a structure as exhibiting any fluorescence. Applicants respectfully traverse the rejection.

At the outset, Applicants note that claims 8, 10, 11, 13, 15 and 16 were amended above to recite that the claimed DNA's encode proteins having serine-tyrosine-glycine or serine-histidine-glycine at positions 65-67. The grouping serine-tyrosine-glycine is described in the specification as forming an imidazolidine ring oxidatively which serves as a chromophore (see paragraph bridging pages 2-3). Therefore, this grouping of amino acids forms an identifiable structure disclosed in the application as contributing to fluorescence.

Similarly, the application discloses numerous mutant proteins containing a mutation in the serine-tyrosine-glycine grouping substituting histidine for the tyrosine at position 65 (see Tables 4). Moreover, the application discloses that mutant proteins having this substitution (Tyr66His) retain fluorescence, and in some cases, exhibit a much higher level of fluorescence. Accordingly, the grouping serine-histidine-glycine at positions 65-67 also forms an identifiable structure disclosed in the application as contributing to fluorescence.

Notwithstanding the amendments to the claims, according to the Written Description Guidelines recently published by the Office (Federal Register, Vol. 66, No. 4, January 5, 2001), the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics (see page 1106 of the Federal Register publication, copy enclosed, column 3). According to the Guidelines, "what constitutes a 'representative number' is an inverse function of the skill in the art [and] depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Furthermore, the Guidelines stress that "[d]escription of a representative number of species does not require that the description be of such specificity that it would provide individual support for each species that the genus embraces."

Applicant respectfully submits that the present application discloses actual reduction to practice of a representative number of species so as to justify the claimed genus. Furthermore, the present application discloses a combination of structural and functional characteristics relating to the claimed proteins that would clearly convey to one of skill in the art that applicant was in possession of the claimed genus at the time of filing. The skill in the art relating to green fluorescence protein (GFP) mutants and mutagenesis procedures in general is quite developed as evidenced by the issued patents of record relating to mutants of GFP. Given that what constitutes a "representative number" of species is an "inverse function of the skill and knowledge in the art" as provided by the Written Description Guidelines, those of skill in the art relating to GFP mutants would recognize in applicant's disclosure a genus of DNA's encoding mutant GFP proteins having at least the mutations recited in the claims.

For instance, claim 11 is directed to a DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1, with at least the mutations of Tyr145Phe, Phe64Leu, and Leu236Arg, said fluorescent protein also having serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His. Applicants disclose actual reduction to practice of at least two mutants - BFP(202) and BFP(205)

having the recited mutations (see Table 4). Moreover, BFP(205) contains the two additional mutations of Val163Ala and Ser175Gly (see Table 4 on page 23). Applicants also show a functional correlation with mutants having at least the three mutations recited, in that the species disclosed exhibit an extremely higher value of fluorescence at 37°C in comparison with BFP(201), which contains only the two mutations Tyr66His and Tyr145Phe (see Table 5). Thus, the application reasonably conveys to one of skill in the art of GFP proteins that there are BFP proteins other than BFP(202), which contains the four mutations recited, that exhibit fluorescence.

In view of the actual reduction to practice of these species within the claimed genus, the functional correlation between the structure of these mutants and a higher fluorescence, and the fact that the skill in the art of GFP mutations is well developed such that the skilled artisan would immediately envision a genus of mutants having the recited mutations, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of written description.

Claims 8, 10, 11, 13 and 15-20 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being allegedly enabling for a fluorescent protein having the amino acid of SEQ ID NO: 1 consisting of the mutations recited in the claims, allegedly fails to enable SEQ ID NO: 1 comprising other mutations in addition to these mutations. In particular, while the Examiner agrees that recombinant and mutagenesis techniques are known, she does not believe that it is "routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure." Applicants respectfully traverse the rejection.

First, Applicants note that the specification does not disclose only one mutant falling within the scope of each claim. For instance, taking claim 11 as an example, in addition to mutant BFP(202), which contains the four mutations recited, Applicants also disclose BFP(205), into which the additional mutations of Val163Ala and Ser175Gly have been introduced (see Table 4 on page 23). Thus, the specification is enabling for other species for claim 11 than a mutant "consisting of" the four recited mutants, because the specification demonstrates actual reduction to practice of other proteins containing further mutations in addition to those recited.

Furthermore, the isolation of more than one protein within the claimed genus provides an expectation that one of skill in the art may successfully identify further mutant proteins within the genus using the methods disclosed in the specification. Indeed, the Application discloses at pages 18-20 a method for randomly introducing mutations into a GFP sequence using Mutagenic PCR, wherein random mutants are screened for increased fluorescence in *E. coli* following UV irradiation. The present inventors isolated and sequenced ten different mutant clones using this procedure, and identified several mutations as listed in Table 1 on page 28. One of skill in the art upon reading applicant's disclosure could readily perform random Mutagenic PCR on BFP(202), for instance, which contains the recited four mutations, and readily screen for random mutants that display fluorescence using the assay disclosed in the specification. Moreover, the skilled artisan would have an expectation of success that proteins containing additional mutations could be isolated given Applicants' identification of BFP(202) and BFP(205) as described above.

Thus, in contrast to what was alleged in the Office Action dated January 10, 2002, the disclosure does provide the expectation that one may successfully obtain other mutants demonstrating fluorescence that contain further mutations in addition to those recited in the claims. Applicant has specifically identified such mutants in the disclosure in the disclosure of

BFP(205), for instance. Further, Applicants have disclosed methods whereby the skilled artisan could readily screen large numbers of random mutants in order to identify those exhibiting increased fluorescence. Given that the disclosure provides an expectation of success in isolating further mutants within the claimed genus, the specification is enabling for the full scope of the claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement is respectfully requested.

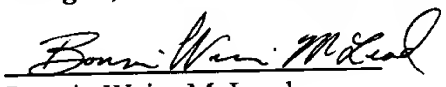
This reply is fully responsive to the Office Action dated January 10, 2002. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,
Morgan, Lewis & Bockius LLP

Dated: July 10, 2002

By: 
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APPENDIX

The following amendments were presented above:

IN THE SPECIFICATION:

The line at page 5, line 23, was amended as follows:

--Thr Ala Ala Gly Ile Thr His Gly Met Asp Glu Leu Tyr Lys (SEQ ID NO: [1]15)--.

IN THE CLAIMS

8. (Twice Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of Phe64Leu, Val163Ala and Ser175Gly, said fluorescent protein having serine-tyrosine-glycine at position Nos. 65-67 of SEQ ID No: 1.

10. (Twice Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of [Tyr66His,] Tyr145Phe and Phe64Leu, said fluorescent protein having serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His.

11. (Twice Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of [Tyr66His,] Tyr145Phe, Phe64Leu, and Leu236Arg, said fluorescent protein having serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His.

13. (Twice Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of [Tyr66His,] Tyr145Phe, Phe64Leu, Val163Ala, Ser175Gly and Leu236Arg, said fluorescent protein having serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His.

15. (Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of Val163Ala and Ser175Gly, said fluorescent protein having serine-tyrosine-glycine at position Nos. 65-67 of SEQ ID No: 1.

16. (Amended) DNA encoding a fluorescent protein comprising the amino acid sequence set forth in SEQ ID No. 1 with at least the mutations of [Tyr66His,] Tyr145Phe, Val163Ala and Ser175Gly, said fluorescent protein having serine-histidine-glycine corresponding to position Nos. 65-67 of SEQ ID No: 1 obtained by mutation Tyr66His.